REMARKS / ARGUMENTS

Claims 1, 2 and 4-11 are pending in the application and stand rejected. By the foregoing amendment, the applicants have added new claim 12. No new matter is added by the amendments. Support for the amendments can be found in the specification as filed, for example on pages 1 and 3. In view of the foregoing amendments and following discussion, the applicants submit that all pending claims are in condition for allowance.

On page 2 of the Office Action the Examiner maintained the rejection of claims 1-2, 4 and 6 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al., (U.S. Pat. No. 6,261,539). The applicants respectfully traverse the rejection. Adjei does not disclose or suggest the invention of claim 1. Adjei teaches only a single active ingredient formulation including albuterol or ipratropium bromide. There is no teaching or suggestion of a combined albuterol sulfate / ipratropium bromide suspension formulation with the claimed ranges of water content. As set forth below, the specific water content of claim 1 provides unexpected superior results in reproducibility of actuation events.

The Examiner has not interpreted the data in the Declaration of George DeStefano ("DeStefano Declaration") properly. The Examiner stated that the claimed range of water of 0.13 to 0.18% in rejected claim 1 is within the disclosed range of 0.03 to 0.2% for water in Adjei and thus a prima facie case of obviousness exists. Furthermore, the Examiner found unpersuasive the previously made argument that the instantly claimed range of 0.13 to 0.18% water resulted in unexpected results. Specifically, the Examiner noted that no unexpected results were shown because there is no significant difference between, for example, cans containing 1000, 1200, 1500 and 2500 ppm water. On page 14 of the Office Action, the Examiner alleges no significant difference exists between the % reproducibility of actuation 1, week 1, of ipratropium bromide, shown in Tables 4-7, of cans containing 1000, 1200, 1500 and 2500 ppm water where the % reproducibility values are 96.17, 99.50, 95.39 and 96.72, respectively, for the inverted-5 can, and 95.13, 101.78, 98.04 and 95.55, respectively, for the upright-5 can. A similar analysis for albuterol sulfate was described by the Examiner on page 15 of the Office Action.

The significant difference is not found when comparing the % reproducibility of ipratropium bromide and albuterol sulfate in one actuation event in various cans having different water contents as the Examiner has done. Rather, the significant difference is shown by comparing the consistency of % reproducibility over a series of actuation events of the same can

(e.g., a can having albuterol sulfate, ipratropium bromide with a 1200 ppm water content) versus the consistency of % reproducibility over a series of actuation events in a different can (e.g., a can having albuterol sulfate, ipratropium bromide with a 1500 ppm water content). When cans of differing water content are compared in this manner, a clear distinction in the consistency of % reproducibility of the amount of albuterol sulfate over a series of actuation events can be observed in cans having water content of 1200 ppm or below, which show inconsistent reproducibility, over those cans having a water content of 1500 – 4000 ppm which show unexpectedly good and consistent reproducibility. The % reproducibility of ipratropium bromide is not affected by water content but that of albuterol is. For the purpose of showing unexpected results, it is irrelevant whether "cans" containing different water contents release the same or different amounts of the active ingredients.

The data submitted in the DeStefano declaration shows that cans having albuterol sulfate, ipratropium bromide with a water content of 1500 to 4000 ppm (equivalent to 0.15 – 0.4% w/w) clearly show significantly better single actuation reproducibility (SAR) of albuterol sulfate released during each actuation event compared to those cans containing albuterol sulfate, ipratropium bromide with a water content of 1200 ppm (equivalent to 0.12% w/w) or less. The first eight tables in Report No. AS/C-03004 (submitted in the DeStefano declaration), show that the SAR of albuterol sulfate is very inconsistent between actuation events in cans containing a water content level ranging from inherent (approximately 300 ppm) to 1200 ppm. For example, in the seventh table showing inverted can 1 with a water content of 1200 ppm, the amount of albuterol sulfate released during consecutive actuation event nos. 129 and 130 is 81.29 and 136.33 % of theory, respectively. The difference in SAR is even more exaggerated in the eighth table showing upright can 1 with a water content of 1200 ppm, where the amount of albuterol sulfate released during consecutive actuation event nos. 129 and 130 is 52.51 and 138.19 % of theory, respectively.

As shown in the ninth to eighteenth tables of Report No. AS/C-03004, the SAR of albuterol sulfate is significantly more consistent over actuation events in cans having a water content of 1500 to 4000 ppm (equivalent to 0.15 - 0.4% w/w). For example, in the ninth table showing inverted can 1 with a water content of 1500 ppm, the amount of albuterol sulfate released during consecutive actuation event nos. 129 and 130 is 113.98 and 118.36 % of theory, respectively. The SAR is just as consistent in the tenth table showing upright can 1 with a water

content of 1500 ppm, where the amount of albuterol sulfate released during consecutive actuation event nos. 129 and 130 is 113.66 and 113.45 % of theory, respectively. Thus, unexpected results are apparent for cans containing a formulation comprising water in an amount of about 0.15 to 0.4%(w/w).

In light of the above discussion, one skilled in the art viewing Adjei would not expect that water content as claimed would have such a profound effect on actuation reproducibility. Water content is not identified in Adjei as an important factor for this characteristic. According to Adjei, the water content can be the same whether the active ingredient is albuterol or ipratropium. One skilled in the art would be led to believe water content is not an important factor in achieving reproducibility. Thus, claim 1 is not obvious in light of Adjei. Claims 2, 4 and 6 which depend from claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On pages 4-8 the Examiner maintained the rejection of claims 1-2, 4 and 6 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. (EP 1219293); over Ashurst et al. (U.S. Pat. No. 6,511,652); and over Keller et al. (U.S. Pat. 6,475,467). The applicants respectfully traverse the rejection. For reasons similar to those discussed above, and those discussed in previous responses incorporated herein by reference, none of the references teach or suggest the claimed invention. Lewis teaches a composition including one or more of salbutamol, ipratropium bromide or other active ingredient, with a water content of 0.1% to 0.5%. Ashurst teaches a metered dose inhaler containing salbutamol and/or ipratropium and/or other active ingredient, with a water content of at least 0.015% and exemplify formulations that contain 0.015% to 0.1% (col. 5, lines 24-39). Keller teaches one or more active ingredients including ipratropium bromide and/or albuterol however, does not teach any range of water content, and only teaches a formulation comprising less than 1% water (col. 3, lines 55-67). None of the references teach or suggest the superiority of the claimed range of water of the invention of claim 1 to result in a significantly better SAR for "cans" containing albuterol sulfate and ipratropium bromide with a water content of 1500 - 4000 ppm to release the same amount of albuterol sulfate (i.e., % of theory) during each single actuation event. None of these references would lead a skilled artisan to conclude the claimed range of water content would have a significant effect on the SAR. Therefore, claim 1 is not obvious over Lewis, Ashurst, or Keller and is allowable.

Claims 2, 4 and 6 which depend from claim 1 are also not obvious and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejections.

On page 9 the Examiner maintained the rejection of claims 5 and 7-11 under 35 U.S.C. § 103(a) as being unpatentable over Adjei et al. in view of Jager et al. (WO 9413262). The applicants respectfully traverse the rejection. The combination of the references does not result in the claimed invention. For reasons similar to those discussed above, Adjei does not teach or suggest the claimed water content of claim 1 that results in unexpected reproducibility as discussed above. Jager fails to cure the deficiency. Jager teaches an ipratropium MDI with a broad range of water content of 0 to 5% but does not teach or suggest the instantly claimed range that results in the unexpected reproducibility. As noted above, the % water content does not appear to affect reproducibility of actuation for ipratropium bromide, therefore Jager is not relevant to claim 1 or claims 5 and 7-11 which depend therefrom. Since the combination of Adjei and Jager does not result in claim 1, dependent claims 5 and 7-11 cannot be obvious over Adjei in view of Jager and are thus allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On page 10 the Examiner maintained the rejection of claims 5 and 7-11 under 35 U.S.C. § 103(a) as being unpatentable over Lewis et al. in view of Jager et al. (WO 9413262). The applicants respectfully traverse the rejection. The combination of the references does not result in the claimed invention. For reasons similar to those discussed above, Lewis does not teach or suggest the claimed water content of claim 1 that results in unexpected reproducibility as discussed above. The deficiencies of Jager are discussed hereinabove. Since the combination of Lewis and Jager does not result in claim 1, dependent claims 5 and 7-11 cannot be obvious over Lewis in view of Jager and are thus allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

On page 16 the Examiner maintained the rejection of claims 1-2, 4-11 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Pat. No. 6,423,298 in view of Adjei et al. The applicants respectfully traverse the rejection. For reasons similar to those discussed above, the claimed invention is not obvious over the combination of the references. The '298 patent discloses a water content ranging from 0.0001 to 10%. The shortcomings of the Adjei reference are discussed above. The combination of the references cannot teach a skilled artisan the claimed water content that results in unexpected

reproducibility as discussed above. Therefore, the combination of the '298 patent and Adjei does not result in the claimed invention. Thus, claims 1, 2 and 4-11 are not obvious over the '298 patent in view of Adjei and are therefore allowable. Accordingly, the applicants respectfully request the Examiner to withdraw the rejection.

Applicants submit that all claims pending in the patent application are in condition for allowance. Accordingly, both reconsideration of this application and its swift passage to issuance are earnestly solicited. The fee for a RCE is submitted herewith. In the event there are any fees due and owing in connection with this matter, please charge same to our Deposit Account No. 11-0223.

Respectfully submitted,

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